Docket No.: 20342/1202529-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Richard Franklin

Application No.: 10/762,566 | Confirmation No.: 3220

Filed: January 23, 2004 | Art Unit: 1614

For: FORMULATION AND METHODS FOR THE TREATMENT OF THROMBOCYTHEMIA | Examiner: A. R. Hughes

DECLARATION OF GUNNAR BIRGEGÅRD, M.D., PH.D. UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Gunnar Birgegård, M.D., Ph.D., do hereby declare and state the following:

1. I am a citizen of Sweden and over 21 years of age.

2. I received a medical degree from Uppsala University, Sweden in 1972 and a Ph.D. from the Faculty of Medicine at Uppsala University in 1979 for my thesis work on ferritin and inflammation.

3. For over 30 years, I have been diagnosing patients, treating patients, teaching, and researching in the area of hematology, including conducting good clinical practices studies on the anagrelide treatment for myeloproliferative disorders. I have authored over 70 peer-reviewed original research articles in the area of hematology, including myeloproliferative disorders, and have co-authored the World Health Organization Blue Book on myeloproliferative disorders. I have been the chairman of the Nordic Study Group for Myeloproliferative Disorders since 1997. I am currently a Full Professor at the Institute for Medical Sciences, Faculty of Medicine at Uppsala

University. I am on the Shire Inc. Advisory Board for anagrelide and am the principle investigator in the EXELS multicenter European study (401), an EMEA-initiated long-term observational follow-up study on the efficacy and safety of anagrelide performed in 12 European countries on behalf of Shire Inc. My curriculum vitae is attached as Exhibit 1 to this declaration.

4. In my expert opinion, *thrombosis* and *thrombocythemia* are distinct entities. Literature and textbooks in the fields of internal medicine and hematology confirm that they are separate entities.

5. *Thrombosis* (a clot in a blood vessel) may occur spontaneously, from unknown causes, or from a long list of specific underlying causes like prolonged bed rest, mechanical obstruction, coagulation disorders etc. *See* Exhibit 2 (Souhami/Moxham, Textbook of Internal Medicine, Churchill-Livingstone, page 1043, table 25.53) listing 15 different causes of thrombosis, among them the myeloproliferative disorders of essential thrombocythemia (ET) and polycythemia vera (PV). In most of these situations, except the myeloproliferative disorders, thrombocytosis is not present and not part of the reason for thrombosis. Thrombosis is treated in the acute phase with low molecular weight heparin and after this for varying periods of time with oral warfarin. Anagrelide is per se not a treatment for an already existing thrombosis.

6. *Thrombocytosis* (thrombocythemia, high platelet count) means an increased number of circulating platelets in the blood stream and may occur either secondary to infection, inflammation, iron deficiency, malignant disease etc. or as part of a myeloproliferative disorder such as ET, myelofibrosis, chronic myelogenous leukemia or PV. These well defined malignant disorders (for diagnostic criteria *see* Exhibit 3 (the WHO Classification 2008)) especially ET and PV, increase the risk for thrombosis both when platelet counts are normal and when there is an increased platelet level. A high platelet level is one of the risk factors used for risk stratification in international and national guidelines for the treatment of myeloproliferative disorders (see for instance Exhibit 4, Italian and Nordic guidelines). On the other hand, thrombocytosis due to other causes, so called secondary thrombocytosis (in inflammation etc) does not increase the risk for thrombosis. In myeloproliferative disease, thrombocytosis may be treated with anagrelide, interferon or cytostatic

punishable by fine or imprisonment or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issued thereupon.

Dated: Jan 30, 2009

Respectfully submitted,

Gunnar Birgegård, M.D., Ph.D.

Exhibit 1. Curriculum Vitae of Gunnar Birgegård, M.D., Ph.D.

Exhibit 2. Souhami/Moxham, Textbook of Internal Medicine, Churchill-Livingstone, page 1043, table 25.53

Exhibit 3. WHO Classification 2008

Exhibit 4. Italian and Nordic guidelines

Formaterat: Teckensnitt:6 pt

EXHIBIT 1

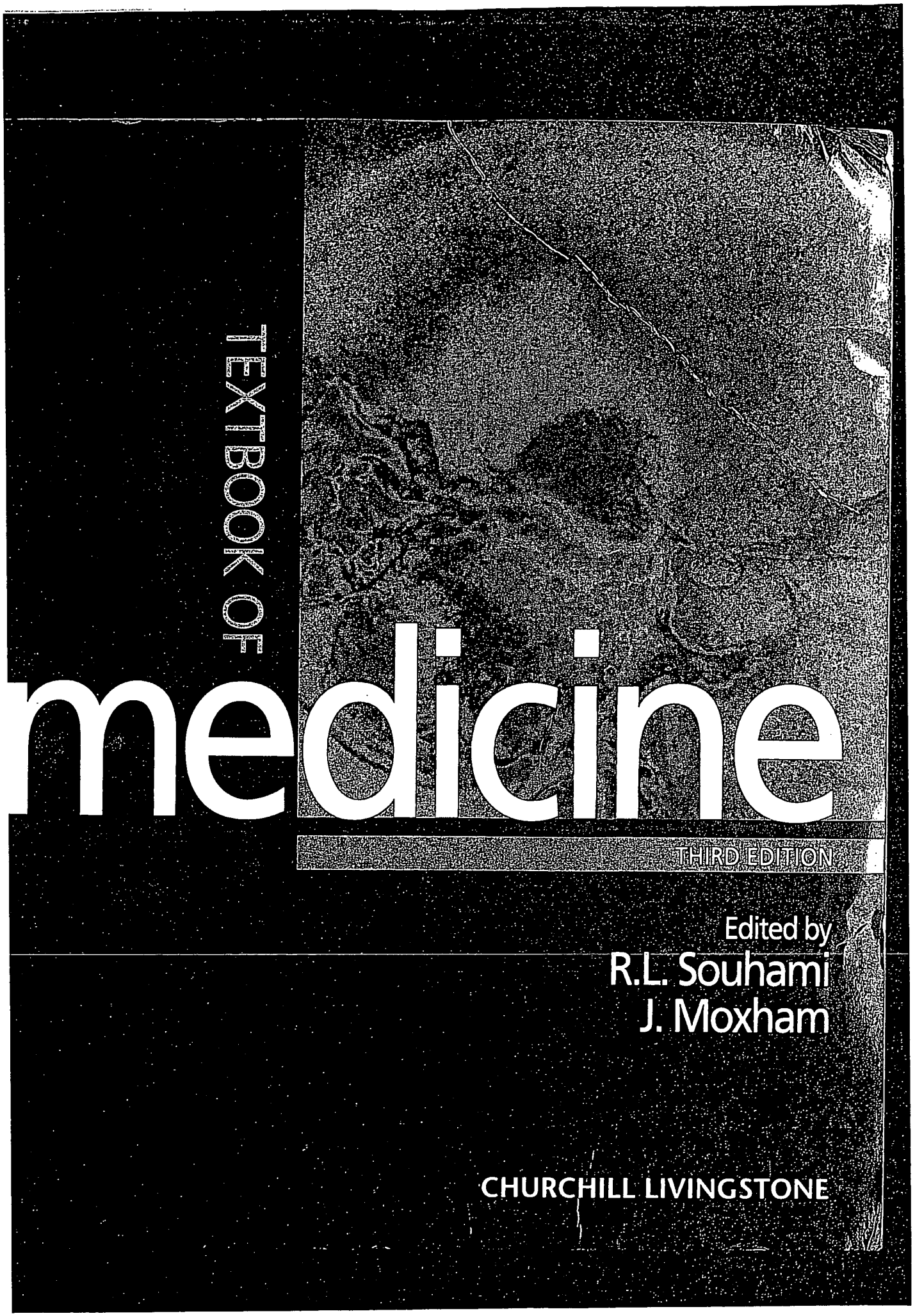
Curriculum vitae

Gunnar S. Birgegård, born Jan 5, 1944

Graduated from Medical School, Uppsala University,Sweden, in 1972
Specialist in internal medicine and hematology 1978
Ph D Inst for Medical Sciences, Faculty of medicine, 1979, thesis on ferritin and inflammation
Employed in the Dept of hematology, University Hospital, Uppsala, Sweden, since 1973
Research fellow at Cardeza Foundation for Hematological Research, Jefferson Medical School, USA, chief Allan Erslev, 1980-1981.
Docent in Internal Medicine, Inst for Medical Sciences, Faculty of medicine, Uppsala University, Sweden, in 1983.
Ass. prof, Senior lecturer, Inst for Medical Sciences, Faculty of medicine, Uppsala University, Sweden since 1983
Full Professor, Inst for Medical Sciences, Faculty of medicine, Uppsala University, Sweden, jan 2002.
Member of the Swedish Soc for Hematology, European Hematology Association, Swedish Soc for Oncology, American Society of Hematology and American Academy on Physician and Patient.
Member of the Society of Living Pedagogues, Sweden (for prize-winning teachers only) .
Course director for the year of Internal Medicine at the Medical School in Uppsala since 1993.
Member of the Curriculum Committee of the Faculty of Medicine, Uppsala University.
The Pedagogical Award of Uppsala University in 1992, The Medical Students´Pedagogical Awards "Glunten" in 1992 and "Lyktan" in 1995.
Director of the Centre for Education, Uppsala Medical School since 2003.
Chairman of the Nordic Study Group for Myeloproliferative Disorders since 1997.
Member of the steering committee for Leukemia Net WP 9 (MPD). Member of the International Working Group for Idiopathic Myelofibrosis (IWG-IMF)
Coauthor of textbooks (separate) on Anemia, Clinical Skills, Palliative Medicine and Care of Cancer Patients.
Coauthor of WHO Blue book on myeloproliferative disorders.
Author of > 70 peer-reviewed original research papers on iron metabolism, erythropoietin pathofysiologi, treatment of anemia, myeloproliferative disorders etc. Frequently invited lecturer on cancer anemia and its treatment as well as chronic myeloproliferative disorders.
GCP studies conducted on rHuEpo treatment in MDS, anagrelide treatment in MPD, GCP studies on rHuEpo+iv iron in cancer anemia and on long term safety of anagrelide.

Relation to Shire Inc
Principal investigator in the EXELS multicenter European study (401).
Advisory Board for anagrelide.

EXHIBIT 2


TEXTBOOK OF
medicine
THIRD EDITION
Edited by
R.L. Souhami
J. Moxham
CHURCHILL LIVINGSTONE

give prophylactic steroids. Hopes that tPA would have equal efficacy and fewer side-effects have not been realised.

Oral fibrinolytic agents

A variety of oral drugs such as the biguanides (e.g. metformin) and anabolic steroids (e.g. stanozolol) increase fibrinolytic activity, and may have occasional value in patients with recurrent venous and arterial thromboses who are on oral anticoagulants. These agents do, however, have major potential side-effects, e.g. hypoglycaemia and masculinisation, unrelated to their fibrinolytic function.

FURTHER READING ON ANTICOAGULANTS AND ANTITHROMBOTIC DRUGS

Roberts B (ed) 1991 British Committee for Standards in Haematology Guidelines on Oral Coagulation. In: Standard Haematology Practice, pp. 73–87. Blackwell Scientific Publications, Oxford

Wood K (ed) 1994 British Committee for Standards in Haematology Guidelines on the use and monitoring of Heparin. In: Standard Haematology Practice 2: pp. 150–165. Blackwell Scientific Publications, Oxford

PRETHROMBOTIC STATES

A *prethrombotic state* is any situation in which there is an increased risk of thromboembolism. Possible causes with examples are shown in Table 25.53.

Table 25.53 Possible causes of a prethrombotic state

Mechanism	Example
Circulatory stasis	
Immobilisation	Prolonged bed rest
Mechanical obstruction	Pelvic tumours
Increased Hct	Polycythaemia
Greatly increased WBC	Chronic myeloid leukaemia
Increased plasma viscosity	Myeloma
Abnormalities of platelet/vessel wall interaction	
Thrombocytosis	Essential thrombocythaemia
Increased platelet aggregability	Diabetes
Decreased vessel wall prostacylin production?	Thrombotic thrombocytopenic purpura
Coagulation abnormalities	
Clotting factors	Increased levels of VIIIC and VIIC associated with risk of coronary death
	Factor V Leiden
Coagulation inhibitors	Antithrombin III deficiency
	Lupus anticoagulant
	Protein C deficiency
	Protein S deficiency
Fibrinolytic abnormalities	
Plasminogen activators	Found in some patients with thrombotic episodes (significance uncertain)
Inhibitors of plasminogen	
Increased antiplasmin	

The full investigation of a potential prethrombotic state is both extremely time-consuming and expensive. All patients presenting with a thromboembolic episode should be thoroughly examined to exclude local causes of circulatory stasis, and systemic diseases associated with hypercoagulability. A full blood count should be performed to exclude polycythaemia or thrombocytosis. Further studies (Table 25.54) are only cost-effective in selected cases. The criteria for selection of patients (Table 25.55) are designed primarily to allow detection of the hereditary prethrombotic states.

Interpretation of the laboratory investigations for a prethrombotic state is not always easy. Firstly, raised clotting factors or increased levels of activated factors may be secondary to a recent (possibly subclinical) thrombosis, rather than the cause of a prethrombotic state. Similarly, increased levels of platelet release products, such as platelet factor 4 (PF4) or β-thromboglobulin (β-TG), within the serum may reflect ongoing thrombosis rather than a primary platelet/vessel wall abnormality. Secondly, many patients requiring investigation will already be taking oral anticoagulants; determining deficiencies of vitamin-K-dependent proteins such as antithrombin III and protein C is then very difficult.

Table 25.54 Investigation of a prethrombotic state

- Full blood count
- Liver function tests
- Analysis of plasma lipids
- Protein electrophoresis to exclude hypergammaglobulinaemia
- Coagulation screen with particular attention to anormalities due to dysfibrinogenaemia, or a lupus anticoagulant
- Euglobin clot lysis time as an index of the fibrinolytic pathway
- Antithrombin III levels
- Factor V Leiden detection
- Protein C levels (also protein S levels if available)
- Platelet aggregometry to detect hyperaggregable platelets

  or
- Measurement of platelet release products (PF4, β-TG) within the plasma

Table 25.55 Possible criteria for the selection of patients for detailed investigation of a prethrombotic state

- Venous thromboembolism before the age of 45 years
- Recurrent venous thrombosis or thrombophlebitis
- Thrombosis in an unusual site, e.g. mesenteric vein
- Unexplained neonatal thrombosis
- Skin necrosis, particularly if on warfarin
- Arterial thrombosis before the age of 30 years
- Relatives of patient with thrombophilic abnormality
- Patients with a clear family history of venous thrombosis
- Patients with recurrent fetal loss, or SLE

EXHIBIT 3

Leukemia (2008) 22, 14–22

www.nature.com/leu

SPOTLIGHT REVIEW

Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms

A Tefferi[1] and JW Vardiman[2]

[1]*Division of Hematology, Mayo Clinic, Rochester, MN, USA and* [2]*Department of Pathology, University of Chicago, Chicago, IL, USA*

Table 1 The 2008 World Health Organization classification scheme for myeloid neoplasms

1. Acute myeloid leukemia
2. Myelodysplastic syndromes (MDS)
3. Myeloproliferative neoplasms (MPN)
   - 3.1 Chronic myelogenous leukemia
   - 3.2 Polycythemia vera
   - 3.3 Essential thrombocythemia
   - 3.4 Primary myelofibrosis
   - 3.5 Chronic neutrophilic leukemia
   - 3.6 Chronic eosinophilic leukemia, not otherwise categorized
   - 3.7 Hypereosinophilic syndrome
   - 3.8 Mast cell disease
   - 3.9 MPNs, unclassifiable

EXHIBIT 4

[haematologica]
2004;89:215-232

Tiziano Barbui
Giovanni Barosi
Alberto Grossi
Luigi Gugliotta
Lucio N. Liberato
Monia Marchetti
M. Gabriella Mazzucconi
Francesco Rodeghiero
Sante Tura

Practice guidelines for the therapy of essential thrombocythemia. A statement from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

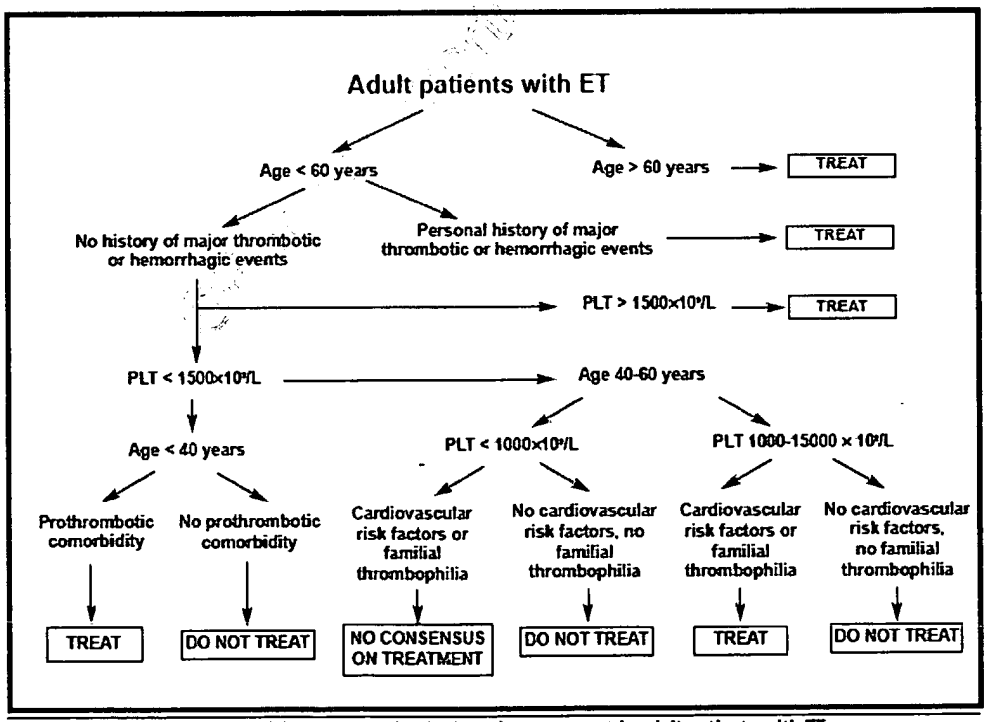


Figure 1. Algorithm for the decision to start platelet-lowering treatment in adult patients with ET.

NORDIC MPD STUDY GROUP

Guidelines for the diagnosis and treatment of patients with polycythemia vera, essential thrombocythemia and primary myelofibrosis.

Guidelines 2008

Page 26:

Summarized recommendations for platelet lowering therapy in ET:

ET patients with age > 60 years and/or patients with a history of previous thromboembolic or hemorrhagic event and/or patients with platelet count >1500x10^9/L should be treated with cytoreductive therapy.
Grade A recommendation, level Ib.

The goal of cytoreductive therapy should be platelets below 400 x10^9/L.
Grade B recommendation, level III.